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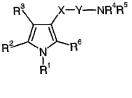
(54) Title: 1,5-DIARYL-PYRROLE-3-CARBOXAMIDE DERIVATIVES AND THEIR USE AS CANNABINOID RECEPTOR MODULATORS



(I)

(57) Abstract: The present invention relates to a compound of formula (I) (A chemical formula should be inserted here - please see paper copy enclosed herewith) in which R^1 and R^2 independently represent phenyl, thienyl or pyridyl each of which is optionally substituted by one, two or three groups represented by *Y*; and R^3 is H, a C_{1-3}alkyl group, a C_{1-3}alkoxymethyl group, trifluoromethyl, a hydroxyC_{1-3}alkyl group, an aminoC_{1-3}alkyl group, C_{1-3}alkoxycarbonyl, carboxy, cyano, carbamoyl, mono or di C_{1-3}alkylcarbamoyl, acetyl, or hydrazinocarbonyl of formula -CONHNR^{a}R^b wherein R^a and R^b are as defined for R^4 and R^5 respectively; X is CO or SO_2 ; Y is absent or represents NH optionally substituted by a C_{1-3}alkyl group; R^4 and R^5 independently represent: a C_{1-5}alkyl group; an (amino)C_{1-3}alkyl- group in which the amino is optionally substituted by one or more C_{1-3}alkyl groups; an optionally substituted non-aromatic C_{3-15}carbocyclic group; a (C_{3-12}cycloalkyl)C_{1-3}alkyl- group; a group -$(CH_2)_t$(phenyl)$_u$; naphthyl; anthracenyl; a saturated 5 to 8 membered heterocyclic group containing one nitrogen and optionally one of the following: oxygen, sulphur or an additional nitrogen wherein the heterocyclic group is optionally substituted ;1-adamantylmethyl; a group - $(CH_2)_v$ Het where Het represents an aromatic heterocycle optionally substituted; or R^4 represents H and R^5 is as defined above; or R^4 and R^5 together with the nitrogen atom to which they are attached represent a saturated 5 to 8 membered heterocyclic group; R^6 is H, a C_{1-3}alkyl group, a C_{1-3}alkoxymethyl group, trifluoromethyl, a hydroxyC_{1-3}alkyl group, C_{1-3}alkoxycarbonyl, carboxy, cyano, carbamoyl, mono or di C_{1-3}alkylcarbamoyl, acetyl, or hydrazinocarbonyl of formula -CONHNR^{a}R^b ; with provisos; to processes for preparing such compounds, to their use in the treatment of obesity, psychiatric and neurological disorders particularly obesity, to methods for their therapeutic use and to pharmaceutical compositions containing them.

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Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

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1,5-DIARYL-PYRROLE-3-CARBOXAMIDE DERIVATIVES AND THEIR USE AS CANNABINOID RECEPTOR MODULATORS

Field of invention

The present invention relates to certain pyrrole carboxamide compounds of formula I, to processes for preparing such compounds, to their use in the treatment of obesity, psychiatric and neurological disorders, and to pharmaceutical compositions containing them.

Background of the invention

It is known that certain CB_1 modulators (known as antagonists or inverse agonists) are useful in the treatment of obesity, psychiatric and neurological disorders (WO01/70700 and EP 656354). However, there is a need for CB_1 modulators with improved physicochemical properties and/or DMPK properties and/or pharmacodynamic properties.

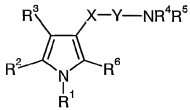
1,5 –Diarylpyrrole-3-carboxamides are reported to have antifungal activity in Il Farmaco 1988, vol XLIII, N9 665, M. Scalzo et al , Il Farmaco 1988, vol 43, N9 677, M. Scalzo et al , Il Farmaco 1989, vol 44, N1 65, C. G. Porretta et al , and Eur.J Med. Chem. 1992, 27, 701 F Cerretto et al. All compounds disclosed in these documents are disclaimed from the compound claims of the present application.

US 6,248,894 discloses certain pyrroles have anti-fungal activity. All compounds disclosed in this document are disclaimed from the compound claims of the present application.

WO01/ 58869 discloses that certain 1-(2-morpholinoethyl)pyrrolecarboxamides are useful in treating respiratory diseases.

Description of the invention

The invention relates to a compound of formula (I)



I

and pharmaceutically acceptable salts, prodrugs, solvates and crystalline forms thereof, in which

R^1 and R^2 independently represent phenyl, thienyl or pyridyl each of which is optionally substituted by one, two or three groups represented by Z;

Z represents a C_{1-3}alkyl group, a C_{1-3}alkoxy group, hydroxy, halo, trifluoromethyl, trifluoromethylthio, difluoromethoxy, trifluoromethoxy, trifluoromethylsulphonyl, nitro, amino, mono or di C_{1-3}alkylamino, mono or di C_{1-3}alkylamido, C_{1-3}alkylsulphonyl, C_{1-3}alkoxycarbonyl, carboxy, cyano, carbamoyl, mono or di C_{1-3}alkyl carbamoyl, sulphamoyl and acetyl; and

R^3 is H, a C_{1-3}alkyl group, a C_{1-3}alkoxymethyl group, trifluoromethyl, a hydroxyC_{1-3}alkyl group, an aminoC_{1-3}alkyl group, C_{1-3}alkoxycarbonyl, carboxy, cyano, carbamoyl, mono or di C_{1-3}alkylcarbamoyl, acetyl, or hydrazinocarbonyl of formula $-CONHR^aR^b$ wherein R^a and R^b are as defined for R^4 and R^5 respectively and;

X is CO or SO_2 ;

Y is absent or represents NH optionally substituted by a C_{1-3}alkyl group;

R^4 and R^5 independently represent :

a C_{1-6}alkyl group;

an (amino)C_{1-4}alkyl– group in which the amino is optionally substituted by one or more C_{1-3}alkyl groups;

an optionally substituted non-aromatic C_{3-15}carbocyclic group;

a (C_{3-12}cycloalkyl)C_{1-3}alkyl– group;

a group $-(CH_2)_r$(phenyl $)_s$ in which r is 0,1, 2, 3 or 4, s is 1 when r is 0 otherwise s is 1 or 2 and the phenyl groups are optionally independently substituted by one, two or three groups represented by Z;

naphthyl;

anthracenyl;

a saturated 5 to 8 membered heterocyclic group containing one nitrogen and optionally one of the following : oxygen, sulphur or an additional nitrogen wherein the heterocyclic group is optionally substituted by one or more C_{1-3}alkyl groups, hydroxy or benzyl ;

1-adamantylmethyl;

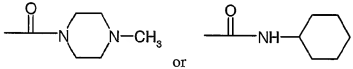
a group $-(CH_2)_t$ Het in which t is 0,1, 2, 3 or 4, and the alkylene chain is optionally substituted by one or more C_{1-3}alkyl groups and Het represents an aromatic heterocycle optionally substituted by one, two or three groups selected from a C_{1-5}alkyl group, a C_{1-5}alkoxy group or halo;

or R^4 represents H and R^5 is as defined above;

or R^4 and R^5 together with the nitrogen atom to which they are attached represent a saturated 5 to 8 membered heterocyclic group containing one nitrogen and optionally one of the following : oxygen, sulphur or an additional nitrogen; wherein the heterocyclic group is optionally substituted by one or more C_{1-3}alkyl groups, hydroxy or benzyl ;

R^6 is H, a C_{1-3}alkyl group, a C_{1-3}alkoxymethyl group, trifluoromethyl, a hydroxyC_{1-3}alkyl group, an aminoC_{1-3}alkyl group, C_{1-3}alkoxycarbonyl, carboxy, cyano, carbamoyl, mono or di C_{1-3}alkylcarbamoyl, acetyl, or hydrazinocarbonyl of formula $-CONHNR^aR^b$ wherein R^a and R^b are as defined for R^4 and R^5 respectively and;

with the proviso that when R^6 is methyl then the group $X\text{-}Y\text{-}NR^4R^5$ does not represent $CONHC_6H_{13}$, $CONHC_{12}H_{25}$, $CONH_2$, $CONHCH_3$, $CON(CH_3)_2$,



or

and with the further proviso that when R^1 and R^2 independently represent phenyl then Z is not an ortho methyl group.

In a particular group of compounds of formula I Z represents a C_{1-3}alkyl group, a C_{1-3}alkoxy group, hydroxy, halo, trifluoromethyl, trifluoromethylthio, difluoromethoxy, trifluoromethoxy, trifluoromethylsulphonyl, amino, mono or di C_{1-3}alkylamino, mono or di C_{1-3}alkylamido, C_{1-3}alkylsulphonyl, C_{1-3}alkoxycarbonyl, carboxy, cyano, carbamoyl, mono or di C_{1-3}alkyl carbamoyl, sulphamoyl and acetyl.

Further values of R^1, R^2, R^3 , $X\text{-}Y\text{-}NR^4R^5$ and R^6 in compounds of formula I now follow. It will be understood that such values may be used where appropriate with any of the definitions, claims or embodiments defined hereinbefore or hereinafter.

In one group of compounds of formula I, R^1 represents phenyl optionally substituted by halo or C_{1-3}alkoxy located in the 2 and 4 positions of the phenyl ring. In such compounds R^1 is selected from phenyl , 4-chlorophenyl, 2, 4-dichlorophenyl and 4-methoxyphenyl.

In a second group of compounds of formula I, R^2 represents phenyl optionally substituted by halo or C_{1-3}alkoxy located in the 2 and 4 positions of the phenyl ring. In such compounds R^1 is selected from phenyl , 2, 4-dichlorophenyl and 2,4-dimethoxyphenyl.

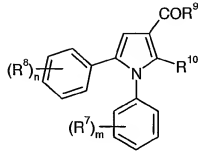
In a third group of compounds of formula I, $X\text{-}Y\text{-}NR^4R^5$ represents CONHPh or CONH(1--piperidyl).

In a fourth group of compounds of formula I, $X\text{-}Y\text{-}NR^4R^5$ represents CONH(1-piperidinyl).

In a fifth group of compounds of formula I, X-Y-NR^4R^5 represents CO(1-piperidinyl).

In a sixth group of compounds of formula I, R^6 represents methyl.

One group of compounds of the present invention relates to compounds of the general formula (II)



II

and pharmaceutically acceptable salts, prodrugs, and solvates in which

m represents 0,1, 2 or 3

R^7 represents a C_{1-6}alkyl group, trifluoromethyl, a C_{1-6}alkoxy group, difluoromethoxy, trifluoromethoxy, or halo wherein when m is 2 or 3 then the groups R^1 may be the same or different;

n represents 0,1, 2 or 3;

R^8 represents a C_{1-6}alkyl group, trifluoromethyl, a C_{1-6}alkoxy group, difluoromethoxy, trifluoromethoxy, or halo wherein when n is 2 or 3 then the groups R^2 may be the same or different;

R^9 represents 1-piperidinyl, 1-piperidinylamino or anilino wherein the phenyl ring is optionally substituted by one or more of the following: a C_{1-6}alkyl group, trifluoromethyl, a C_{1-6}alkoxy group, difluoromethoxy, trifluoromethoxy or halo; and

R^{10} represents a C_{1-6}alkyl, C_{1-6}alkoxy, or a C_{1-6}alkylamino group;

with the proviso that the compound is not 1-{[1-(4-chlorophenyl)-5-phenyl-2-methyl-1*H*-pyrrol-3-yl]carbonyl}piperidine or 1-{[1-(2,4-dichlorophenyl)-5-phenyl-2-methyl-1*H*-pyrrol-3-yl]carbonyl}piperidine.

Further values of R^7, R^8, R^9, R^{10} in compounds of formula I now follow. It will be understood that such values may be used where appropriate with any of the definitions, claims or embodiments defined hereinbefore or hereinafter.

In one group of compounds of formula II, m is 2 and the groups R^7 are located in the 2 and 4 positions of the phenyl ring. In such compounds R^7 is selected from chloro and methoxy and the groups R^7 may be the same or different.

In a second group of compounds of formula II, n is 2 and the groups R^8 are located in the 2 and 4 positions of the phenyl ring. In such compounds R^8 is selected from chloro and methoxy and the groups R^8 may be the same or different.

In a third group of compounds of formula II, R^9 represents anilino.

In a fourth group of compounds of formula II, R^9 represents 1-piperidinyl.

In a fifth group of compounds of formula II, R^9 represents 1-piperidinylamino.

In a sixth group of compounds of formula II, R^{10} represents methyl.

"Pharmaceutically acceptable salt", where such salts are possible, include pharmaceutically acceptable acid addition salt. A suitable pharmaceutically acceptable salt of a compound of Formula I is, for example, an acid-addition salt of a compound of Formula I which is sufficiently basic, for example an acid-addition salt with an inorganic or organic acid such as hydrochloric, hydrobromic, sulphuric, trifluoroacetic, citric or maleic acid.

Throughout the specification and the appended claims, a given chemical formula or name shall encompass all stereo and optical isomers and racemates thereof as well as mixtures in different proportions of the separate enantiomers, where such isomers and enantiomers exist, as well as pharmaceutically acceptable salts thereof and solvates thereof such as for instance hydrates. Isomers may be separated using conventional techniques, e.g. chromatography or fractional crystallisation. The enantiomers may be isolated by separation of racemate for example by fractional crystallisation, resolution or HPLC. The diastereomers may be isolated by separation of isomer mixtures for instance by fractional crystallisation, HPLC or flash chromatography. Alternatively the stereoisomers may be made by chiral synthesis from chiral starting materials under conditions which will not cause racemisation or epimerisation, or by derivatisation, with a chiral reagent. All stereoisomers are included within the scope of the invention.

The following definitions shall apply throughout the specification and the appended claims. Unless otherwise stated or indicated, the term "alkyl" denotes either a straight or branched alkyl group. Examples of said alkyl include methyl, ethyl, n-propyl, isopropyl, n-butyl, iso-butyl, sec-butyl and t-butyl. Preferred alkyl groups are methyl, ethyl, propyl, isopropyl and tertiary butyl.

Unless otherwise stated or indicated, the term "alkoxy" denotes a group O-alkyl, wherein alkyl is as defined above.

Unless otherwise stated or indicated, the term "halo" shall mean fluorine, chlorine, bromine or iodine.

Specific compounds of the invention are:

2-methyl-*N*,1,5-triphenyl-1*H*-pyrrole-3-carboxamide;

1-(4-chlorophenyl)-2-methyl-*N*,5-diphenyl-1*H*-pyrrole-3-carboxamide;

1-(4-methoxyphenyl)-2-methyl-*N*,5-diphenyl-1*H*-pyrrole-3-carboxamide;

5-(2,4-dichlorophenyl)-2-methyl-*N*,1-diphenyl-1*H*-pyrrole-3-carboxamide;

1-(4-chlorophenyl)-5-(2,4-dichlorophenyl)-2-methyl-*N*-phenyl-1*H*-pyrrole-3-carboxamide;

5-(2,4-dichlorophenyl)-1-(4-methoxyphenyl)-2-methyl-*N*-phenyl-1*H*-pyrrole-3-carboxamide;

5-(2,4-dimethoxyphenyl)-2-methyl-*N*,1-diphenyl-1*H*-pyrrole-3-carboxamide;

1-(4-chlorophenyl)-5-(2,4-dimethoxyphenyl)-2-methyl-*N*-phenyl-1*H*-pyrrole-3-carboxamide;

5-(2,4-dimethoxyphenyl)-1-(4-methoxyphenyl)-2-methyl-*N*-phenyl-1*H*-pyrrole-3-carboxamide;

2-methyl-1,5-diphenyl-*N*-piperidin-1-yl-1*H*-pyrrole-3-carboxamide;

1-(4-chlorophenyl)-2-methyl-5-phenyl-*N*-piperidin-1-yl-1*H*-pyrrole-3-carboxamide;

1-(4-methoxyphenyl)-2-methyl-5-phenyl-*N*-piperidin-1-yl-1*H*-pyrrole-3-carboxamide;

5-(2,4-dichlorophenyl)-2-methyl-1-phenyl-*N*-piperidin-1-yl-1*H*-pyrrole-3-carboxamide;

1-(4-chlorophenyl)-5-(2,4-dichlorophenyl)-2-methyl-*N*-piperidin-1-yl-1*H*-pyrrole-3-carboxamide;

5-(2,4-dichlorophenyl)-1-(4-methoxyphenyl)-2-methyl-*N*-piperidin-1-yl-1*H*-pyrrole-3-carboxamide;

1-{[5-(2,4-dimethoxyphenyl)-2-methyl-1-phenyl-1*H*-pyrrol-3-yl]carbonyl}piperidine;

1-(4-chlorophenyl)-5-(2,4-dimethoxyphenyl)-2-methyl-*N*-piperidin-1-yl-1*H*-pyrrole-3-carboxamide; and

5-(2,4-dimethoxyphenyl)-1-(4-methoxyphenyl)-2-methyl-*N*-piperidin-1-yl-1*H*-pyrrole-3-carboxamide;

1-[(2-methyl-1,5-diphenyl-1*H*-pyrrol-3-yl)carbonyl]piperidine;

1-{[1-(4-methoxyphenyl)-2-methyl-5-phenyl-1*H*-pyrrol-3-yl]carbonyl}piperidine;

1-{[5-(2,4-dichlorophenyl)-2-methyl-1-phenyl-1*H*-pyrrol-3-yl]carbonyl}piperidine;

1-{[1-(4-chlorophenyl)-5-(2,4-dichlorophenyl)-2-methyl-1*H*-pyrrol-3-yl]carbonyl}piperidine;

1-{[5-(2,4-dichlorophenyl)-1-(4-methoxyphenyl)-2-methyl-1*H*-pyrrol-3-yl]carbonyl}piperidine;

1-{[1-(4-chlorophenyl)-5-(2,4-dimethoxyphenyl)-2-methyl-1*H*-pyrrol-3-yl]carbonyl}piperidine; and

1-{[5-(2,4-dimethoxyphenyl)-1-(4-methoxyphenyl)-2-methyl-1*H*-pyrrol-3-yl]carbonyl}piperidine;

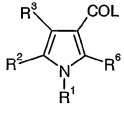
and where applicable, optical isomers, tautomers, stereoisomers and racemates thereof as well as pharmaceutically acceptable salts, solvates and crystalline forms thereof.

It should be understood that the present invention includes each of the above compounds and any combination of two or more these compounds that is 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24 or 25 of these compounds.

Methods of preparation

The compounds of the invention may be prepared as outlined below according to any of the following methods. However, the invention is not limited to these methods, the compounds may also be prepared as described for structurally related compounds in the prior art.

Compounds of formula I in which X is CO may be prepared by reacting a compound of formula III



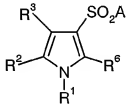
III

in which R^1, R^2, R^3, and R^6 are as previously defined and L represents hydroxy or halo e.g.chloro, with an amine of formula IV

$$R^4R^5YNH_2 \qquad IV$$

in which R^4 and R^5 are as previously defined in an inert solvent, for example dichloromethane, and optionally in the presence of a catalyst, for example a basic catalyst, eg 4-dimethylamino-pyridine, or optionally in the presence of a base for example triethylamine, at a temperature in the range of -25°C to 150°C, and when L is hydroxy optionally in the presence of a coupling agent, for example a carbodiimide, eg 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide.

Compounds of formula I in which X is SO_2 may be prepared by reacting a compound of formula V



V

in which R^1, R^2, R^3 and R^6 are as previously defined and A represents halo with an amine of formula IV

$$R^4R^5YNH_2 \qquad IV$$

in an inert solvent, for example dichloromethane, and optionally in the presence of a catalyst, for example a basic catalyst, eg 4-dimethylamino-pyridine, at a temperature in the range of -25°C to 150°C.

Compounds of formula III may be prepared as described in the Examples and by other methods known to those skilled in the art. Certain compounds of formula III are novel and are claimed as a further aspect of the present invention as useful intermediates.

The compounds of the invention may be isolated from their reaction mixtures using conventional techniques.

Persons skilled in the art will appreciate that, in order to obtain compounds of the invention in an alternative and in some occasions, more convenient manner, the individual process steps mentioned hereinbefore may be performed in a different order, and/or the individual reactions may be performed at a different stage in the overall route (i.e. chemical transformations may be performed upon different intermediates to those associated hereinbefore with a particular reaction).

The expression "inert solvent" refers to a solvent which does not react with the starting materials, reagents, intermediates or products in a manner which adversely affects the yield of the desired product.

Pharmaceutical preparations

The compounds of the invention will normally be administered via the oral, parenteral, intravenous, intramuscular, subcutaneous or in other injectable ways, buccal, rectal, vaginal, transdermal and/or nasal route and/or via inhalation, in the form of pharmaceutical preparations comprising the active ingredient either as a free base, or a pharmaceutically acceptable organic or inorganic acid addition salt, in a pharmaceutically acceptable dosage form. Depending upon the disorder and patient to be treated and the route of administration, the compositions may be administered at varying doses.

Suitable daily doses of the compounds of the invention in the therapeutic treatment of humans are about 0.001-10 mg/kg body weight, preferably 0.01-1 mg/kg body weight.

Oral formulations are preferred particularly tablets or capsules which may be formulated by methods known to those skilled in the art to provide doses of the active compound in the range of 0.5mg to 500mg for example 1 mg, 3 mg, 5 mg, 10 mg, 25mg, 50mg, 100mg and 250mg.

A compound of the invention may also be combined with other anti-obesity agents such as Orlistat or a monoamine reuptake inhibitor, for example Sibutramine. Furthermore, a compound of the invention may also be combined with therapeutic agents that are useful in the treatment of disorders or conditions associated with obesity (such as type II diabetes, metabolic syndrome, dyslipidemia, impaired glucose tolerance, hypertension, coronary heart disease, non-alcoholic steatorheic hepatitis, osteoarthritis and some cancers) and psychiatric and neurological conditions.

According to a further aspect of the invention there is also provided a pharmaceutical formulation including any of the compounds of the invention, or pharmaceutically acceptable derivatives thereof, in admixture with pharmaceutically acceptable adjuvants, diluents and/or carriers.

Pharmacological properties

The compounds of formula (I) are useful for the treatment of obesity, psychiatric disorders such as psychotic disorders, schizophrenia, bipolar disorders, anxiety, anxio-depressive disorders, depression, cognitive disorders, memory disorders, obsessive-compulsive disorders,

anorexia, bulimia, attention disorders like ADHD, epilepsy, and related conditions, and neurological disorders such as dementia, neurological disorders(e.g. Multiple Sclerosis), Raynaud's syndrome, Parkinson's disease, Huntington's chorea and Alzheimer's disease. The compounds are also potentially useful for the treatment of immune, cardiovascular, reproductive and endocrine disorders, septic shock and diseases related to the respiratory and gastrointestinal systems (e.g. diarrhea). The compounds are also potentially useful as agents in treatment of extended abuse, addiction and/or relapse indications, e.g. treating drug (nicotine, ethanol, cocaine, opiates, etc) dependence and/or treating drug (nicotine, ethanol, cocaine, opiates, etc) withdrawal symptoms. The compounds may also eliminate the increase in weight which normally accompanies the cessation of smoking.

In another aspect the present invention provides a compound of formula I as claimed in any previous claim for use as a medicament.

In a further aspect the present invention provides the use of a compound of formula I including the compounds in the provisos in the preparation of a medicament for the treatment or prophylaxis of obesity, psychiatric disorders such as psychotic disorders, schizophrenia, bipolar disorders, anxiety, anxio-depressive disorders, depression, cognitive disorders, memory disorders, obsessive-compulsive disorders, anorexia, bulimia, attention disorders like ADHD, epilepsy, and related conditions, neurological disorders such as dementia, neurological disorders (e.g. Multiple Sclerosis), Parkinson's Disease, Huntington's Chorea and Alzheimer's Disease, immune, cardiovascular, reproductive and endocrine disorders, septic shock, diseases related to the respiratory and gastrointestinal systems (e.g. diarrhea), and extended abuse, addiction and/or relapse indications, e.g. treating drug (nicotine, ethanol, cocaine, opiates, etc) dependence and/or treating drug (nicotine, ethanol, cocaine, opiates, etc) withdrawal symptoms.

In a still further aspect the present invention provides a method of treating obesity, psychiatric disorders such as psychotic disorders such as schizophrenia and bipolar disorders, anxiety, anxio-depressive disorders, depression, cognitive disorders, memory disorders, obsessive-compulsive disorders, anorexia, bulimia, attention disorders like ADHD, epilepsy, and related conditions, neurological disorders such as dementia, neurological disorders (e.g. Multiple Sclerosis), Parkinson's Disease, Huntington's Chorea and Alzheimer's Disease, immune, cardiovascular, reproductive and endocrine disorders, septic shock, diseases related to the respiratory and gastrointestinal systems (e.g. diarrhea), and extended abuse, addiction and/or relapse indications, e.g. treating drug (nicotine, ethanol, cocaine, opiates, etc) dependence

and/or treating drug (nicotine, ethanol, cocaine, opiates, etc) withdrawal symptoms comprising administering a pharmacologically effective amount of a compound of formula I including the compounds in the provisos to a patient in need thereof.

The compounds of the present invention are particulary suitable for the treatment of obesity, e.g. by reduction of appetite and body weight, maintenance of weight reduction and prevention of rebound.

Combination Therapy

The compounds of the invention may be combined with another therapeutic agent that is useful in the treatment of disorders associated with the development and progress of obesity such as hypertension, hyperlipidaemias, dyslipidaemias, diabetes and atherosclerosis. For example, a compound of the present invention may be used in combination with a compound that affects thermogenesis, lipolysis, fat absorption, satiety, or gut motility. The compounds of the invention may be combined with another therapeutic agent that decreases the ratio of LDL:HDL or an agent that causes a decrease in circulating levels of LDL-cholesterol. In patients with diabetes mellitus the compounds of the invention may also be combined with therapeutic agents used to treat complications related to micro-angiopathies.

The compounds of the invention may be used alongside other therapies for the treatment of obesity and its associated complications the metabolic syndrome and type 2 diabetes, these include biguanide drugs, insulin (synthetic insulin analogues) and oral antihyperglycemics (these are divided into prandial glucose regulators and alpha-glucosidase inhibitors).

In another aspect of the invention, the compound of formula I, or a pharmaceutically acceptable salt thereof may be administered in association with a PPAR modulating agent. PPAR modulating agents include but are not limited to a PPAR alpha and/or gamma agonist, or pharmaceutically acceptable salts, solvates, solvates of such salts or prodrugs thereof. Suitable PPAR alpha and/or gamma agonists, pharmaceutically acceptable salts, solvates, solvates of such salts or prodrugs thereof are well known in the art.

In addition the combination of the invention may be used in conjunction with a sulfonylurea.

The present invention also includes a compound of the present invention in combination with a cholesterol-lowering agent. The cholesterol-lowering agents referred to in this application include but are not limited to inhibitors of HMG-CoA reductase (3-hydroxy-3-methylglutaryl coenzyme A reductase). Suitably the HMG-CoA reductase inhibitor is a statin

In the present application, the term "cholesterol-lowering agent" also includes chemical modifications of the HMG-CoA reductase inhibitors, such as esters, prodrugs and metabolites, whether active or inactive.

The present invention also includes a compound of the present invention in combination with an inhibitor of the ileal bile acid transport system (IBAT inhibitor). The present invention also includes a compound of the present invention in combination with a bile acid binding resin.

The present invention also includes a compound of the present invention in combination with a bile acid sequestering agent, for example colestipol or cholestyramine or cholestagel

According to an additional further aspect of the present invention there is provided a combination treatment comprising the administration of an effective amount of a compound of the formula I, or a pharmaceutically acceptable salt thereof, optionally together with a pharmaceutically acceptable diluent or carrier, with the simultaneous, sequential or separate administration one or more of the following agents selected from:

a CETP (cholesteryl ester transfer protein) inhibitor;

a cholesterol absorption antagonist;

a MTP (microsomal transfer protein) inhibitor ;

a nicotinic acid derivative, including slow release and combination products;

a phytosterol compound ;

probucol;

an anti-coagulant;

an omega-3 fatty acid ;

another anti-obesity compound;

an antihypertensive compound for example an angiotensin converting enzyme (ACE) inhibitor, an angiotensin II receptor antagonist, an andrenergic blocker, an alpha andrenergic blocker, a beta andrenergic blocker, a mixed alpha/beta andrenergic blocker, an andrenergic stimulant, calcium channel blocker, an AT-1 blocker, a saluretic, a diuretic or a vasodilator;

a Melanin concentrating hormone (MCH) antagonist;

a PDK inhibitor; or

modulators of nuclear receptors for example LXR, FXR, RXR, and RORalpha;

an SSRI;

a serotonin antagonist;

or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, optionally together with a pharmaceutically acceptable diluent or carrier to a warm-blooded animal, such as man in need of such therapeutic treatment.

Therefore in an additional feature of the invention, there is provided a method for for the treatment of obesity and its associated complications in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of a compound of formula I, or a pharmaceutically acceptable salt thereof in simultaneous, sequential or separate administration with an effective amount of a compound from one of the other classes of compounds described in this combination section, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof.

Therefore in an additional feature of the invention, there is provided a method of treating hyperlipidemic conditions in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of a compound of formula I, or a pharmaceutically acceptable salt thereof in simultaneous, sequential or separate administration with an effective amount of a compound from one of the other classes of compounds described in this combination section or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof.

According to a further aspect of the invention there is provided a pharmaceutical composition which comprises a compound of formula I, or a pharmaceutically acceptable salt thereof, and a compound from one of the other classes of compounds described in this combination section or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, in association with a pharmaceutically acceptable diluent or carrier.

According to a further aspect of the present invention there is provided a kit comprising a compound of formula I, or a pharmaceutically acceptable salt thereof, and a compound from one of the other classes of compounds described in this combination section or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof.

According to a further aspect of the present invention there is provided a kit comprising:

a) a compound of formula I, or a pharmaceutically acceptable salt thereof, in a first unit dosage form;

b) a compound from one of the other classes of compounds described in this combination section or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof; in a second unit dosage form; and

c) container means for containing said first and second dosage forms.

According to a further aspect of the present invention there is provided a kit comprising:

a) a compound of formula I, or a pharmaceutically acceptable salt thereof, together with a pharmaceutically acceptable diluent or carrier, in a first unit dosage form;

b) a compound from one of the other classes of compounds described in this combination section or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, in a second unit dosage form; and

c) container means for containing said first and second dosage forms.

According to another feature of the invention there is provided the use of a compound of the formula I, or a pharmaceutically acceptable salt thereof, and one of the other compounds described in this combination section, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, in the manufacture of a medicament for use in the the treatment of obesity and its associated complications in a warm-blooded animal, such as man.

According to another feature of the invention there is provided the use of a compound of the formula I, or a pharmaceutically acceptable salt thereof, and one of the other compounds described in this combination section, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, in the manufacture of a medicament for use in the treatment of hyperlipidaemic conditions in a warm-blooded animal, such as man.

According to a further aspect of the present invention there is provided a combination treatment comprising the administration of an effective amount of a compound of the formula I, or a pharmaceutically acceptable salt thereof, optionally together with a pharmaceutically acceptable diluent or carrier, with the simultaneous, sequential or separate administration of an effective amount of one of the other compounds described in this combination section, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, optionally together with a pharmaceutically acceptable diluent or carrier to a warm-blooded animal, such as man in need of such therapeutic treatment.

Furthermore, a compound of the invention may also be combined with therapeutic agents that are useful in the treatment of disorders or conditions associated with obesity (such as type II diabetes, metabolic syndrome, dyslipidemia, impaired glucose tolerance, hypertension, coronary heart disease, non-alcoholic steatorheic hepatitis, osteoarthritis and some cancers) and psychiatric and neurological conditions.

Examples

The invention will now be described in more detail with the following examples that are not to be construed as limiting the invention.

Abbreviations

DCM - dichloromethane

DMF - dimethylformamide

DMAP - 4-dimethylaminopyridine

EDC - 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide

TEA – triethylamine

TFA – trifluoroacetic acid

DMSO	dimethyl sulfoxide
t	triplet
s	singlet
d	doublet
q	quartet
qvint	quintet
m	multiplet
br	broad
bs	broad singlet
dm	doublet of multiplet
bt	broad triplet
dd	doublet of doublets

General Experimental Procedures

Mass spectra were recorded on either a Micromass ZQ single quadrupole or a Micromass LCZ single quadrupole mass spectrometer both equipped with a pneumatically assisted electrospray interface (LC-MS). ^{1}H NMR measurements were performed on a Varian Inova 500, operating at ^{1}H frequency 500 MHz. Chemical shifts are given in ppm. Purifications were performed on a semipreparative HPLC with a mass triggered fraction collector, Shimadzu QP 8000 single quadrupole mass spectrometer equipped with 19 x 100 mm C8 column. As the mobile phase, acetonitrile and buffered phase (0.1 M NH_4Ac:acetonitrile 95:5) were used.

Alternatively ^{1}H NMR and ^{13}C NMR measurements were performed on a Varian Mercury 300 or Varian UNITY plus 400, 500 or 600 spectrometers, operating at ^{1}H frequencies of 300, 400, 500 and 600 MHz, respectively, and at ^{13}C frequencies of 75, 100, 125 and 150 MHz, respectively. Measurements were made on the delta scale (δ).

Unless otherwise stated, chemical shifts are given in ppm with the solvent as internal standard.

Synthesis of intermediates

Preparation A

The following intermediates were prepared according to Scalzo, M. et al., Farmaco, Ed. Sci. (1988), 43(9), 665-676.

(a) Ethyl 2-acetyl-4-oxo-4-phenylbutanoate

^{1}H-NMR ($(CD_3)_2SO$) δ 7.98 (d, 2H), 7.65 (t, 1H), 7.53 (t, 2H), 4.13 (m, 3H), 3.56 (ddd, 2H), 2.32 (s, 3H), 1.18 (t, 3H).

(b) Ethyl 2-acetyl-4-(2,4-dichlorophenyl)-4-oxobutanoate

^{1}H-NMR ($(CD_3)_2SO$) δ 7.81-7.54 (m, 3H), 4.20-4.10 (m, 3H), 3.52-3.39 (m, 2H), 2.30 (s, 3H), 1.18 (t, 3H).

(c) Ethyl 2-acetyl-4-(2,4-dimethoxyphenyl)-4-oxobutanoate

^{1}H-NMR ($(CD_3)_2SO$) δ 7.68 (dd, 1H), 6.67 (s, 1H), 6.61 (m, 1H), 4.10 (m, 3H), 3.91, (d, 3H), 3.84 (d, 3H), 3.41 (m, 2H), 2.28 (d, 3H), 1.17 (dt, 3H). MS *m/z* 309 $(M+H)^+$.

Preparation B

The following intermediates were prepared essentially as described: Scalzo, M. et al., Farmaco, Ed. Sci. (1988), 43(9), 665-676. As recognised by those skilled in the art, the

compounds described in Preparation A were, together with the appropriately substituted aniline, used as starting materials.

(a) Ethyl 2-methyl-1,5-diphenyl-1*H*-pyrrole-3-carboxylate

Toluene-4-sulphonic acid monohydrate (13 mg, 0.075 mmol) was added under nitrogen to a solution of aniline (0.43 mL, 4.7 mmol) and ethyl 2-acetyl-4-oxo-4-phenylbutanoate (Preparation A (a), 1.16 g, 4.7 mmol) in ethanol (55 mL). The mixture was refluxed for 20h, then evaporated. The crude product (1.22 g) was used in the next step without further purification. MS *m/z* 306 $(M+H)^+$.

(b) Ethyl 1-(4-chlorophenyl)-2-methyl-5-phenyl-1*H*-pyrrole-3-carboxylate

The title compound was prepared as described in Preparation B (a).

The crude product (1.61 g) was used in the next step without further purification. MS *m/z* 340 $(M+H)^+$.

(c) Ethyl 1-(4-methoxyphenyl)-2-methyl-5-phenyl-1*H*-pyrrole-3-carboxylate

The title compound was prepared as described in Preparation B (a).

The crude product (1.68 g) was used in the next step without further purification MS *m/z* 336 $(M+H)^+$.

(d) Ethyl 5-(2,4-dichlorophenyl)-2-methyl-1-phenyl-1*H*-pyrrole-3-carboxylate

The title compound was prepared as described in Preparation B (a).

The crude product (0.55 g) was used in the next step without further purification. MS *m/z* 374 $(M+H)^+$.

(e) Ethyl 1-(4-chlorophenyl)-5-(2,4-dichlorophenyl)-2-methyl-1*H*-pyrrole-3-carboxylate

The title compound was prepared as described in Preparation B (a).

The crude product (1.32 g) was used in the next step without further purification. MS *m/z* 408 $(M+H)^+$.

(f) Ethyl 5-(2,4-dichlorophenyl)- 1-(4-methoxyphenyl)-2-methyl-1*H*-pyrrole-3-carboxylate

The title compound was prepared as described in Preparation B (a).

The crude product (0.72 g) was used in the next step without further purification. MS *m/z* 404 $(M+H)^+$.

(g) Ethyl 5-(2,4-dimethoxyphenyl)-2-methyl-1-phenyl-1*H*-pyrrole-3-carboxylate

The title compound was prepared as described in Preparation B (a).

The crude product (0.33 g) was used in the next step without further purification. MS *m/z* 366 $(M+H)^+$.

(h) Ethyl 1-(4-chlorophenyl)-5-(2,4-dimethoxyphenyl)-2-methyl-1*H*-pyrrole-3-carboxylate

The title compound was prepared as described in Preparation B (a).

The crude product (0.36 g) was used in the next step without further purification. MS *m/z* 400 $(M+H)^+$.

(i) Ethyl 5-(2,4-dimethoxyphenyl)-1-(4-methoxyphenyl)-2-methyl-1*H*-pyrrole-3-carboxylate

The title compound was prepared as described in Preparation B (a).

The crude product (0.37 g) was used in the next step without further purification. MS *m/z* 396 $(M+H)^+$.

Preparation C

The title compounds described in Preparation B (a-i) were used as starting materials for the compounds described in Preparation C (a-i)

(a) 2-Methyl-1,5-diphenyl-1*H*-pyrrole-3-carboxylic acid

Sodium hydroxide (2.4 g, 60 mmol) was added to a solution of crude ethyl 2-methyl-1,5-diphenyl-1*H*-pyrrole-3-carboxylate (from Preparation B (a), 1.22 g, 4.0 mmol) in ethanol (25 mL). The mixture was refluxed for 3h, then an additional portion of sodium hydroxide (0.20 g, 5.0 mmol) was added and the mixture was refluxed for an additional 90 min. The ethanol was evaporated, then HCl (75 mL, 2M aq) was added and the mixture was stirred for 7h. The acidic aqueous solution was extracted with EtOAc, the organic layer was washed with brine, dried ($MgSO_4$), filtrated and concentrated to give the crude product (0.95 g). The crude product was used in the next step without further purification. MS *m/z* 278 $(M+H)^+$.

(b) 1-(4-Chlorophenyl)-2-methyl-5-phenyl-1*H*-pyrrole-3-carboxylic acid

The title compound was prepared as described in Preparation C (a).

The crude product (1.2 g) was used in the next step without further purification. MS *m/z* 312 $(M+H)^+$.

(c) 1-(4-Methoxyphenyl)-2-methyl-5-phenyl-1*H*-pyrrole-3-carboxylic acid

The title compound was prepared as described in Preparation C (a).

The crude product (1.3 g) was used in the next step without further purification. MS *m/z* 308 $(M+H)^+$.

(d) 5-(2,4-Dichlorophenyl)-2-methyl-1-phenyl-1*H*-pyrrole-3-carboxylic acid

The title compound was prepared as described in Preparation C (a).

The crude product (0.44 g) was used in the next step without further purification. MS *m/z* 346 $(M+H)^+$.

(e) 1-(4-Chlorophenyl)-5-(2,4-dichlorophenyl)-2-methyl-1*H*-pyrrole-3-carboxylic acid

The title compound was prepared as described in Preparation C (a).

The crude product (1.12 g) was used in the next step without further purification. MS *m/z* 380 $(M+H)^+$.

(f) 5-(2,4-Dichlorophenyl)-1-(4-methoxyphenyl)-2-methyl-1*H*-pyrrole-3-carboxylic acid

The title compound was prepared as described in Preparation C (a).

The crude product (0.51 g) was used in the next step without further purification. MS *m/z* 376 $(M+H)^+$.

(g) 5-(2,4-Dimethoxyphenyl)-2-methyl-1-phenyl-1*H*-pyrrole-3-carboxylic acid

The title compound was prepared as described in Preparation C (a).

The crude product (0.26 g) was used in the next step without further purification. MS *m/z* 338 $(M+H)^+$.

(h) 1-(4-Chlorophenyl)-5-(2,4-dimethoxyphenyl)-2-methyl-1*H*-pyrrole-3-carboxylic acid

The title compound was prepared as described in Preparation C (a).

The crude product (0.30 g) was used in the next step without further purification. MS *m/z* 372 $(M+H)^+$.

(i) 5-(2,4-Dimethoxyphenyl)-1-(4-methoxyphenyl)-2-methyl-1*H*-pyrrole-3-carboxylic acid

The title compound was prepared as described in Preparation C (a).

The crude product (0.34 g) was used in the next step without further purification. MS *m/z* 368 $(M+H)^+$.

Examples of the invention

Example 1

2-Methyl-*N*,1,5-triphenyl-1*H*-pyrrole-3-carboxamide

The crude 2-methyl-1,5-diphenyl-1*H*-pyrrole-3-carboxylic acid (50 mg, 0.18 mmol) from Preparation C (a) and 4-dimethylaminopyridine (10 mg, 0.08 mmol) were dissolved in CH_2Cl_2 (2 mL) and DMF (0.030 mL). The solution was cooled to 0°C. A slurry of 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (76 mg, 0.40 mmol) in CH_2Cl_2 (0.5 mL) and DMF (0.040 mL) was added dropwise. Aniline (0.046 mL, 0.49 mmol) in CH_2Cl_2 (0.5 mL) and was then added dropwise. The mixture was allowed to attain room temperature, and was stirred overnight. The mixture was diluted with CH_2Cl_2, washed with Na_2HCO_3 (sat, aq) and the phases were separated. The organic phase was concentrated and the residue was purified by semipreparative HPLC to give the title compound (33 mg, 52%).

^{1}H-NMR (CD_3OD) δ 7.65 (dd, 2H), 7.44 (m, 3H), 7.33 (t, 2H), 7.20 (m, 2H), 7.16-7.08 (m, 6H), 6.90 (s, 1H), 2.38 (s, 3H). MS *m/z* 353 $(M+H)^+$.

Example 2

1-(4-Chlorophenyl)-2-methyl-*N*,5-diphenyl-1*H*-pyrrole-3-carboxamide

Crude 1-(4-chlorophenyl)-2-methyl-5-phenyl-1*H*-pyrrole-3-carboxylic acid from Preparation C (b) was used as described in Example 1 to give the title compound (31 mg, 50%). ^{1}H-NMR (CD_3OD) δ 7.65 (d, 2H), 7.45 (m, 2H), 7.33 (t, 2H), 7.22-7.08 (m, 8H), 6.90 (s, 1H), 2.40 (s, 3H). MS *m/z* 387 $(M+H)^+$.

Example 3

1-(4-methoxyphenyl)-2-methyl-*N*,5-diphenyl-1*H*-pyrrole-3-carboxamide

Crude 1-(4-methoxyphenyl)-2-methyl-5-phenyl-1*H*-pyrrole-3-carboxylic acid from Preparation C (c) was used as described in Example 1 to give the title compound (20 mg, 32%). ^{1}H-NMR (CD_3OD) δ 7.65 (d, 2H), 7.33 (t, 2H), 7.18-7.08 (m, 8H), 6.97 (m, 2H), 6.88 (s, 1H), 3.82 (s, 3H), 2.37 (s, 3H). MS *m/z* 383 $(M+H)^+$.

Example 4

5-(2,4-dichlorophenyl)-2-methyl-*N*,1-diphenyl-1*H*-pyrrole-3-carboxamide

Crude 5-(2,4-dichlorophenyl)-2-methyl-1-phenyl-1*H*-pyrrole-3-carboxylic acid from Preparation C (d) was used as described in Example 1 to give the title compound (9 mg, 15%). ^{1}H-NMR (CD_3OD) δ 7.64 (dd, 2H), 7.39-7.30 (m, 6H), 7.23 (d, 1H), 7.17 (m, 3H), 7.10 (dt, 1H), 6.84 (s, 1H), 2.40 (s, 3H). MS *m/z* 421 $(M+H)^+$.

Example 5

1-(4-Chlorophenyl)-5-(2,4-dichlorophenyl)-2-methyl-*N*-phenyl-1*H*-pyrrole-3-carboxamide

Crude 1-(4-chlorophenyl)-5-(2,4-dichlorophenyl)-2-methyl-1*H*-pyrrole-3-carboxylic acid from Preparation C (e) was used as described in Example 1 to give the title compound (3 mg, 5%). ^{1}H-NMR (CD_3OD) δ 7.64 (dd, 2H), 7.41-7.36 (m, 3H), 7.32 (t, 2H), 7.27 (d, 1H), 7.23 (dd, 1H), 7.17 (m, 2H), 7.10 (t, 1H), 6.85 (s, 1H), 2.42 (s, 3H). MS *m/z* 455 $(M+H)^+$.

Example 6

5-(2,4-Dichlorophenyl)-1-(4-methoxyphenyl)-2-methyl-*N*-phenyl-1*H*-pyrrole-3-carboxamide

Crude 5-(2,4-dichlorophenyl)-1-(4-methoxyphenyl)-2-methyl-1*H*-pyrrole-3-carboxylic acid from Preparation C (f) was used as described in Example 1 to give the title compound (15 mg, 25%). ^{1}H-NMR (CD_3OD) δ 7.64 (dd, 2H), 7.38 (d, 1H), 7.32 (t, 2H), 7.22 (t, 1H), 7.19 (dd, 1H), 7.09 (m, 3H), 6.89 (m, 2H), 6.82 (s, 1H), 3.78 (s, 3H), 2.38 (s, 3H). MS *m/z* 451 $(M+H)^+$.

Example 7

5-(2,4-Dimethoxyphenyl)-2-methyl-*N*,1-diphenyl-1*H*-pyrrole-3-carboxamide

Crude 5-(2,4-dimethoxyphenyl)-2-methyl-1-phenyl-1*H*-pyrrole-3-carboxylic acid from Preparation C (g) was used as described in Example 1 to give the title compound (20 mg, 33%). ^{1}H-NMR (CD_3OD) δ 7.64 (dd, 2H), 7.36-7.24 (m, 5H), 7.15-7.06 (m, 4H), 6.65(s, 1H), 6.43 (dd, 1H), 6.28 (d, 1H), 3.73 (s, 3H), 3.42 (s, 3H), 2.38 (s, 3H). MS *m/z* 413 $(M+H)^+$.

Example 8

1-(4-Chlorophenyl)-5-(2,4-dimethoxyphenyl)-2-methyl-*N*-phenyl-1*H*-pyrrole-3-carboxamide

Crude 1-(4-chlorophenyl)-5-(2,4-dimethoxyphenyl)-2-methyl-1*H*-pyrrole-3-carboxylic acid from Preparation C (h) was used as described in Example 1 to give the title compound (39 mg, 65%). ^{1}H-NMR (CD_3OD) δ 7.63 (d, 2H), 7.32 (m, 4H), 7.17-7.06 (m, 4H), 6.65(s, 1H), 6.46 (dd, 1H), 6.31 (d, 1H), 3.75 (s, 3H), 3.44 (s, 3H), 2.39 (s, 3H). MS *m/z* 447 $(M+H)^+$.

Example 9

5-(2,4-Dimethoxyphenyl)-1-(4-methoxyphenyl)-2-methyl-*N*-phenyl-1*H*-pyrrole-3-carboxamide

Crude 5-(2,4-dimethoxyphenyl)-1-(4-methoxyphenyl)-2-methyl-1*H*-pyrrole-3-carboxylic acid from Preparation C (i) was used as described in Example 1 to give the title compound (44 mg, 73%). ^{1}H-NMR (CD_3OD) δ 7.63 (d, 2H), 7.32 (t, 2H), 7.09 (m, 2H), 7.00 (d, 2H), 6.85 (d, 2H), 6.62(s, 1H), 6.42 (dd, 1H), 6.31 (d, 1H), 3.77 (s, 3H), 3.73 (s, 3H), 3.48 (s, 3H), 2.36 (s, 3H). MS *m/z* 443 $(M+H)^+$.

Example 10a

2-Methyl-1,5-diphenyl-*N*-piperidin-1-yl-1*H*-pyrrole-3-carboxamide

and Example 10b

1-[(2-Methyl-1,5-diphenyl-1*H*-pyrrol-3-yl)carbonyl]piperidine

The crude 2-methyl-1,5-diphenyl-1*H*-pyrrole-3-carboxylic acid (236 mg, 0.85 mmol) from Preparation C (a) and 4-dimethylaminopyridine (47 mg, 0.38 mmol) were dissolved in CH_2Cl_2 (5 mL) and DMF (0.142 mL) and 1-aminopiperidine (0.218 mL, 2.18 mmol) was added. The solution was cooled to 0°C. A slurry of 1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide hydrochloride (360 mg, 01.88 mmol) in CH_2Cl_2 (2.4 mL) and DMF (0.189 mL) was added dropwise. The mixture was allowed to attain room temperature, and was stirred overnight. The mixture was diluted with CH_2Cl_2, washed with Na_2HCO_3 (sat, aq) and the phases were separated. The organic phase was concentrated and the residue was purified by semipreparative HPLC to give 10a (20 mg, 7%), and 10b (91 mg, 31%).

10a had: ^{1}H-NMR (CD_3OD) δ 7.41 (m, 3H), 7.20-7.04 (m, 7H), 6.68 (s, 1H), 2.84 (brs, 4H), 2.32 (s, 3H), 1.74 (m, 4H), 1.46 (brs, 2H). MS *m/z* 360 $(M+H)^+$.

10b had: ^{1}H-NMR (CD_3OD) δ 7.41 (m, 3H), 7.20-7.04 (m, 7H), 6.37 (s, 1H), 3.70 (t, 4H), 2.32 (s, 3H), 1.74 (m, 2H), 1.65 (brs, 4H). MS *m/z* 345 $(M+H)^+$.

Example 11a

1-(4-Chlorophenyl)-2-methyl-5-phenyl-*N*-piperidin-1-yl-1*H*-pyrrole-3-carboxamide and Example 11b

1-{[1-(4-Chlorophenyl)-2-methyl-5-phenyl-1*H*-pyrrol-3-yl]carbonyl}piperidine

Crude 1-(4-chlorophenyl)-2-methyl-5-phenyl-1*H*-pyrrole-3-carboxylic acid from Preparation C (b) was used as described in Example 10 to give the title compounds 11a (7 mg, 2%), and 11b (129 mg, 35%).

11a had: ^{1}H-NMR (CD_3OD) δ 7.43 (m, 2H), 7.20-7.04 (m, 7H), 6.67 (s, 1H), 2.83 (brs, 4H), 2.34 (s, 3H), 1.74 (m, 4H), 1.46 (brs, 2H). MS *m/z* 394 $(M+H)^+$.

11b had: ^{1}H-NMR (CD_3OD) δ 7.43 (m, 2H), 7.20-7.04 (m, 7H), 6.37 (s, 1H), 3.68 (t, 4H), 2.12 (s, 3H), 1.74 (m, 2H), 1.64 (brs, 4H). MS *m/z* 379 $(M+H)^+$.

Example 12a

1-(4-Methoxyphenyl)-2-methyl-5-phenyl-*N*-piperidin-1-yl-1*H*-pyrrole-3-carboxamide And Example 12b

1-{[1-(4-Methoxyphenyl)-2-methyl-5-phenyl-1*H*-pyrrol-3-yl]carbonyl}piperidine

Crude 1-(4-methoxyphenyl)-2-methyl-5-phenyl-1*H*-pyrrole-3-carboxylic acid from Preparation C (c) was used as described in Example 10 to give the title compounds 12a (43 mg, 10%), and 12b (174 mg, 43%).

12a had: ^{1}H-NMR (CD_3OD) δ 7.16-7.05 (m, 7H), 6.96 (d, 2H), 6.66 (s, 1H), 3.81 (s, 3H), 2.83 (brs, 4H), 2.50 (s, 3H), 1.74 (m, 4H), 1.45 (brs, 2H). MS *m/z* 390 $(M+H)^+$.

12b had: ^{1}H-NMR (CD_3OD) δ 7.16-7.05 (m, 7H), 6.95 (d, 2H), 6.35 (s, 1H), 3.81 (s, 3H), 3.70 (brs, 4H), 2.10 (s, 3H), 1.74 (m, 2H), 1.64 (brs, 4H). MS *m/z* 375 $(M+H)^+$.

Example 13a

5-(2,4-Dichlorophenyl)-2-methyl-1-phenyl-*N*-piperidin-1-yl-1*H*-pyrrole-3-carboxamide and Example 13b

1-{[5-(2,4-Dichlorophenyl)-2-methyl-1-phenyl-1*H*-pyrrol-3-yl]carbonyl}piperidine

Crude 5-(2,4-dichlorophenyl)-2-methyl-1-phenyl-1*H*-pyrrole-3-carboxylic acid from Preparation C (d) was used as described in Example 10 to give the title compounds 13a (7 mg, 3%), and 13b (52 mg, 20%).

13a had: ^{1}H-NMR (CD_3OD) δ 7.37-7.30 (m, 4H), 7.20-7.10 (m, 4H), 6.61 (s, 1H), 2.82 (brs, 4H), 2.35 (s, 3H), 1.73 (t, 4H), 1.45 (brs, 2H). MS *m/z* 428 $(M+H)^+$.

13b had: ^{1}H-NMR (CD_3OD) δ 7.38-7.30 (m, 4H), 7.15 (m, 4H), 6.34 (s, 1H), 3.70 (t, 4H), 2.15 (s, 3H), 1.75 (t, 2H), 1.64 (brs, 4H). MS *m/z* 413 $(M+H)^+$.

Example 14a

1-(4-Chlorophenyl)-5-(2,4-dichlorophenyl)-2-methyl-*N*-piperidin-1-yl-1*H*-pyrrole-3-carboxamide

and Example 14b 1-{[1-(4-Chlorophenyl)-5-(2,4-dichlorophenyl)-2-methyl-1*H*-pyrrol-3-yl]carbonyl}piperidine

Crude 1-(4-chlorophenyl)-5-(2,4-dichlorophenyl)-2-methyl-1*H*-pyrrole-3-carboxylic acid from Preparation C (e) was used as described in Example 10 to give the title compounds 14a (17 mg, 3%), and 14b (144 mg, 22%).

14a had: ^{1}H-NMR (CD_3OD) δ 7.36 (m, 3H), 7.22 (s, 2H), 7.13 (m, 2H), 6.62 (s, 1H), 2.80 (brs, 4H), 2.35 (s, 3H), 1.72 (t, 4H), 1.44 (brs, 2H). MS *m/z* 462 $(M+H)^+$.

14b had: ^{1}H-NMR (CD_3OD) δ 7.37 (m, 3H), 7.20 (s, 2H), 7.15 (d, 2H), 6.34 (s, 1H), 3.69 (t, 4H), 2.15 (s, 3H), 1.73 (m, 2H), 1.62 (brs, 4H). MS *m/z* 447 $(M+H)^+$.

Example 15a

5-(2,4-Dichlorophenyl)-1-(4-methoxyphenyl)-2-methyl-*N*-piperidin-1-yl-1*H*-pyrrole-3-carboxamide

and Example 15b 1-{[5-(2,4-Dichlorophenyl)-1-(4-methoxyphenyl)-2-methyl-1*H*-pyrrol-3-yl]carbonyl}piperidine

Crude 5-(2,4-dichlorophenyl)-1-(4-methoxyphenyl)-2-methyl-1*H*-pyrrole-3-carboxylic acid from Preparation C (f) was used as described in Example 10 to give the title compounds 15a (24 mg, 8%), and 15b (69 mg, 23%).

15a had: ^{1}H-NMR (CD_3OD) δ 7.36 (s, 1H), 7.17 (s, 2H), 7.04 (d, 2H), 6.87 (d, 2H), 6.58 (s, 1H), 3.76 (s, 3H), 2.82 (brs, 4H), 2.37 (s, 3H), 1.72 (m, 4H), 1.44 (brs, 2H). MS *m/z* 458 $(M+H)^+$.

15b had: ^{1}H-NMR (CD_3OD) δ 7.37 (s, 1H), 7.15 (s, 2H), 7.06 (m, 2H), 6.88 (m, 2H), 6.31 (s, 1H), 3.77 (s, 3H), 3.69 (t, 4H), 2.13 (s, 3H), 1.73 (m, 2H), 1.62 (brs, 4H). MS *m/z* 443 $(M+H)^+$.

Example 16

1-{[5-(2,4-Dimethoxyphenyl)-2-methyl-1-phenyl-1*H*-pyrrol-3-yl]carbonyl}piperidine

Crude 5-(2,4-dimethoxyphenyl)-2-methyl-1-phenyl-1*H*-pyrrole-3-carboxylic acid from Preparation C (g) was used as described in Example 10 to give the title compound (83 mg, 54%).

^{1}H-NMR (CD_3OD) δ 7.34-7.20 (m, 3H), 7.07 (m, 3H), 6.40 (m, 1H), 6.27 (s, 1H), 6.15 (s, 1H), 3.70 (m, 7H), 3.39 (s, 3H), 2.14 (s, 3H), 1.73 (m, 2H), 1.63 (brs, 4H). MS *m/z* 405 $(M+H)^+$.

Example 17a

1-(4-Chlorophenyl)-5-(2,4-dimethoxyphenyl)-2-methyl-*N*-piperidin-1-yl-1*H*-pyrrole-3-carboxamide and Example 17b 1-{[1-(4-Chlorophenyl)-5-(2,4-dimethoxyphenyl)-2-methyl-1*H*-pyrrol-3-yl]carbonyl}piperidine

Crude 1-(4-chlorophenyl)-5-(2,4-dimethoxyphenyl)-2-methyl-1*H*-pyrrole-3-carboxylic acid from Preparation C (h) was used as described in Example 10 to give the title compounds 17a (4 mg, 7%) and 17b (47 mg, 27%).

^{1}H-NMR (CD_3OD) for 17a: δ 7.31 (d, 2H), 7.07 (m, 3H), 6.43 (m, 2H), 6.30 (s, 1H), 3.74 (s, 3H), 3.41 (s, 3H), 2.80 (brs, 4H), 2.33 (s, 3H), 1.72 (m, 4H), 1.44 (brs, 2H). MS *m/z* 454 $(M+H)^+$.

^{1}H-NMR (CD_3OD) for 17b: δ 7.32 (d, 2H), 7.07 (m, 3H), 6.44 (m, 1H), 6.30 (s, 1H), 6.15 (s, 1H), 3.74 (s, 3H), 3.69 (m, 4H), 3.41 (s, 3H), 2.14 (s, 3H), 1.72 (m, 2H), 1.62 (brs, 4H). MS *m/z* 439 $(M+H)^+$.

Example 18a

5-(2,4-Dimethoxyphenyl)-1-(4-methoxyphenyl)-2-methyl-*N*-piperidin-1-yl-1*H*-pyrrole-3-carboxamide

and Example 18b 1-{[5-(2,4-Dimethoxyphenyl)-1-(4-methoxyphenyl)-2-methyl-1*H*-pyrrol-3-yl]carbonyl}piperidine

Crude 5-(2,4-dimethoxyphenyl)-1-(4-methoxyphenyl)-2-methyl-1*H*-pyrrole-3-carboxylic acid from Preparation C (i) was used as described in Example 10 to give the title compounds 18a (45 mg, 22%), and 18b (92 mg, 56%).

18a had: ^{1}H-NMR (CD_3OD) δ 7.04 (d, 1H), 6.97 (m, 2H), 6.84 (m, 2H), 6.40 (m, 2H), 6.29 (d, 1H), 3.76 (s, 3H), 3.74 (s, 3H), 3.48 (s, 3H), 2.82 (brs, 4H), 2.40 (s, 3H), 1.72 (m, 4H), 1.44 (brs, 2H). MS *m/z* 450 $(M+H)^+$.

18b had: ^{1}H-NMR (CD_3OD) δ 7.03 (d, 1H), 6.98 (m, 2H), 6.84 (m, 2H), 6.40 (dd, 1H), 6.30 (d, 1H), 6.11 (s, 1H), 3.75 (s, 3H), 3.72 (s, 3H), 3.69 (brs, 4H), 3.46 (s, 3H), 2.11 (s, 3H), 1.73 (m, 2H), 1.62 (brs, 4H). MS *m/z* 435 $(M+H)^+$.

Pharmacological Activity

Compounds of the present invention are active against the receptor product of the CB1 gene. The affinity of the compounds of the invention for central cannabinoid receptors is demonstrable in methods described in Devane et al , Molecular Pharmacology, 1988, 34,605 or those described in WO01/70700 or EP 656354. Alternatively the assay may be performed as follows.

10μg of membranes prepared from cells stably transfected with the CB1 gene were suspended in 200μl of 100mM NaCl, 5mM $MgCl_2$, 1mM EDTA, 50mM HEPES (pH 7.4), 1mM DTT, 0.1% BSA and 100μM GDP. To this was added an EC80 concentration of agonist (CP55940), the required concentration of test compound and 0.1μCi [^{35}S]-GTPγS. The reaction was allowed to proceed at 30°C for 45 min. Samples were then transferred on to GF/B filters using a cell harvester and washed with wash buffer (50mM Tris (pH 7.4), 5mM $MgCl_2$, 50mM NaCl). Filters were then covered with scintilant and counted for the amount of [^{35}S]-GTPγS retained by the filter.

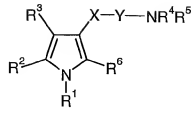
Activity is measured in the absence of all ligands (minimum activity) or in the presence of an EC80 concentration of CP55940 (maximum activity). These activities are set as 0% and 100% activity respectively. At various concentrations of novel ligand, activity is calculated as a percentage of the maximum activity and plotted. The data are fitted using the equation

y=A+((B-A)/1+((C/x) ÙD)) and the IC50 value determined as the concentration required to give half maximal inhibition of GTPγS binding under the conditions used.

The compounds of the present invention are active at the CB1 receptor (IC50 <1 micromolar). Most preferred compounds have IC50 <200 nanomolar.

Claims:

1. A compound of formula (I)



I

and pharmaceutically acceptable salts, prodrugs and solvates thereof, in which

R^1 and R^2 independently represent phenyl, thienyl or pyridyl each of which is optionally substituted by one, two or three groups represented by Z;

Z represents a C_{1-3}alkyl group, a C_{1-3}alkoxy group, hydroxy, halo, trifluoromethyl, trifluoromethylthio, difluoromethoxy, trifluoromethoxy, trifluoromethylsulphonyl, amino, mono or di C_{1-3}alkylamino, mono or di C_{1-3}alkylamido, C_{1-3}alkylsulphonyl, C_{1-3}alkoxycarbonyl, carboxy, cyano, carbamoyl, mono or di C_{1-3}alkyl carbamoyl, sulphamoyl and acetyl; and

R^3 is H, a C_{1-3}alkyl group, a C_{1-3}alkoxymethyl group, trifluoromethyl, an aminoC_{1-3}alkyl group, a hydroxyC_{1-3}alkyl group, C_{1-3}alkoxycarbonyl, carboxy, cyano, carbamoyl, mono or di C_{1-3}alkylcarbamoyl, acetyl, or hydrazinocarbonyl of formula $-CONHNR^aR^b$ wherein R^a and R^b are as defined for R^4 and R^5 respectively and;

X is CO or SO_2 ;

Y is absent or represents NH optionally substituted by a C_{1-3}alkyl group;

R^4 and R^5 independently represent :

a C_{1-6}alkyl group;

an (amino)C_{1-4}alkyl– group in which the amino is optionally substituted by one or more C_{1-3}alkyl groups;

an optionally substituted non-aromatic C_{3-15}carbocyclic group;

a (C_{3-12}cycloalkyl)C_{1-3}alkyl– group;

a group $-(CH_2)_r(\text{phenyl})_s$ in which r is 0,1, 2, 3 or 4, s is 1 when r is 0 otherwise s is 1 or 2 and the phenyl groups are optionally independently substituted by one, two or three groups represented by Z;

naphthyl;

anthracenyl;

a saturated 5 to 8 membered heterocyclic group containing one nitrogen and optionally one of the following : oxygen, sulphur or an additional nitrogen wherein the heterocyclic group is optionally substituted by one or more C_{1-3}alkyl groups, hydroxy or benzyl ;

1-adamantylmethyl;

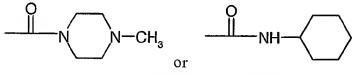
a group $-(CH_2)_t$ Het in which t is 0,1, 2, 3 or 4, and the alkylene chain is optionally substituted by one or more C_{1-3}alkyl groups and Het represents an aromatic heterocycle optionally substituted by one, two or three groups selected from a C_{1-5}alkyl group, a C_{1-5}alkoxy group or halo;

or R^4 represents H and R^5 is as defined above;

or R^4 and R^5 together with the nitrogen atom to which they are attached represent a saturated 5 to 8 membered heterocyclic group containing one nitrogen and optionally one of the following : oxygen, sulphur or an additional nitrogen; wherein the heterocyclic group is optionally substituted by one or more C_{1-3}alkyl groups, hydroxy or benzyl ;

R^6 is H, a C_{1-3}alkyl group, a C_{1-3}alkoxymethyl group, trifluoromethyl, a hydroxyC_{1-3}alkyl group, C_{1-3}alkoxycarbonyl, carboxy, cyano, carbamoyl, mono or di C_{1-3}alkylcarbamoyl, acetyl, or hydrazinocarbonyl of formula $-CONHNR^aR^b$ wherein R^a and R^b are as defined for R^4 and R^5 respectively and;

with the proviso that when R^6 is methyl then the group $X\text{-}Y\text{-}NR^4R^5$ does not represent $CONHC_8H_{13}$, $CONHC_{12}H_{25}$, $CONH_2$, $CONHCH_3$, $CON(CH_3)_2$,



or

and with the further proviso that when R^1 and R^2 independently represent phenyl then Z is not an ortho methyl group.

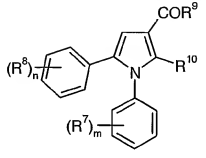
2. A compound according to claim 1 in which R^1 represents phenyl optionally substituted by halo or C_{1-3}alkoxy located in the 2 and 4 positions of the phenyl ring.

3. A compound according to any previous claim in which R^2 represents phenyl optionally substituted by halo or C_{1-3}alkoxy located in the 2 and 4 positions of the phenyl ring.

4. A compound according to any previous claim in which X-Y-NR^4R^5 represents CONHPh or CONH(1–piperidyl).

5. A compound according to any previous claim in which R^6 represents methyl.

6. A compound according to claim 1 of the general formula (II) in which



II

and pharmaceutically acceptable salts, prodrugs, and solvates in which

m represents 0,1, 2 or 3

R^7 represents a C_{1-6}alkyl group, trifluoromethyl, a C_{1-6}alkoxy group, difluoromethoxy, trifluoromethoxy, or halo wherein when m is 2 or 3 then the groups R^1 may be the same or different;

n represents 0,1, 2 or 3;

R^8 represents a C_{1-6}alkyl group, trifluoromethyl, a C_{1-6}alkoxy group, difluoromethoxy, trifluoromethoxy, or halo wherein when n is 2 or 3 then the groups R^2 may be the same or different;

R^9 represents 1-piperidinyl, 1-piperidinylamino or anilino wherein the phenyl ring is optionally substituted by one or more of the following: a C_{1-6}alkyl group, trifluoromethyl, a C_{1-6}alkoxy group, difluoromethoxy, trifluoromethoxy or halo; and

R^{10} represents a C_{1-6}alkyl, C_{1-6}alkoxy, or a C_{1-6}alkylamino group;

with the proviso that the compound is not 1-{[1-(4-chlorophenyl)-5-phenyl-2-methyl-1*H*-pyrrol-3-yl]carbonyl}piperidine or 1-{[1-(2,4-dichlorophenyl)-5-phenyl-2-methyl-1*H*-pyrrol-3-yl]carbonyl}piperidine.

7. A compound according to claim 6 in which m is 2 and the groups R^7 are located in the 2 and 4 positions of the phenyl ring.

8. A compound according to claim 6 or claim 7 in which n is 2 and the groups R^8 are located in the 2 and 4 positions of the phenyl ring. In a third group of compounds of formula II, R^9 represents anilino.

9. A compound according to any one of claims 6, 7 or 8 in which R^9 represents 1-piperidinyl.

10. A compound according to any one of claims 6, 7, 8 or 9 in which R^9 represents 1-piperidinylamino.

11. A compound according to any one of claims 6, 7, 8, 9 or 10 in which R^{10} represents methyl.

12. A compound selected from one or more of the following:

2-methyl-*N*,1,5-triphenyl-1*H*-pyrrole-3-carboxamide;

1-(4-chlorophenyl)-2-methyl-*N*,5-diphenyl-1*H*-pyrrole-3-carboxamide;

1-(4-methoxyphenyl)-2-methyl-*N*,5-diphenyl-1*H*-pyrrole-3-carboxamide;

5-(2,4-dichlorophenyl)-2-methyl-*N*,1-diphenyl-1*H*-pyrrole-3-carboxamide;

1-(4-chlorophenyl)-5-(2,4-dichlorophenyl)-2-methyl-*N*-phenyl-1*H*-pyrrole-3-carboxamide;

5-(2,4-dichlorophenyl)-1-(4-methoxyphenyl)-2-methyl-*N*-phenyl-1*H*-pyrrole-3-carboxamide;

5-(2,4-dimethoxyphenyl)-2-methyl-*N*,1-diphenyl-1*H*-pyrrole-3-carboxamide;

1-(4-chlorophenyl)-5-(2,4-dimethoxyphenyl)-2-methyl-*N*-phenyl-1*H*-pyrrole-3-carboxamide;

5-(2,4-dimethoxyphenyl)-1-(4-methoxyphenyl)-2-methyl-*N*-phenyl-1*H*-pyrrole-3-carboxamide;

2-methyl-1,5-diphenyl-*N*-piperidin-1-yl-1*H*-pyrrole-3-carboxamide;

1-(4-chlorophenyl)-2-methyl-5-phenyl-*N*-piperidin-1-yl-1*H*-pyrrole-3-carboxamide;

1-(4-methoxyphenyl)-2-methyl-5-phenyl-*N*-piperidin-1-yl-1*H*-pyrrole-3-carboxamide;

5-(2,4-dichlorophenyl)-2-methyl-1-phenyl-*N*-piperidin-1-yl-1*H*-pyrrole-3-carboxamide;

1-(4-chlorophenyl)-5-(2,4-dichlorophenyl)-2-methyl-*N*-piperidin-1-yl-1*H*-pyrrole-3-carboxamide;

5-(2,4-dichlorophenyl)-1-(4-methoxyphenyl)-2-methyl-*N*-piperidin-1-yl-1*H*-pyrrole-3-carboxamide;

1-{[5-(2,4-dimethoxyphenyl)-2-methyl-1-phenyl-1*H*-pyrrol-3-yl]carbonyl}piperidine;

1-(4-chlorophenyl)-5-(2,4-dimethoxyphenyl)-2-methyl-*N*-piperidin-1-yl-1*H*-pyrrole-3-carboxamide; and

5-(2,4-dimethoxyphenyl)-1-(4-methoxyphenyl)-2-methyl-*N*-piperidin-1-yl-1*H*-pyrrole-3-carboxamide;

1-[(2-methyl-1,5-diphenyl-1*H*-pyrrol-3-yl)carbonyl]piperidine;

1-{[1-(4-methoxyphenyl)-2-methyl-5-phenyl-1*H*-pyrrol-3-yl]carbonyl}piperidine;

1-{[5-(2,4-dichlorophenyl)-2-methyl-1-phenyl-1*H*-pyrrol-3-yl]carbonyl}piperidine;

1-{[1-(4-chlorophenyl)-5-(2,4-dichlorophenyl)-2-methyl-1*H*-pyrrol-3-yl]carbonyl}piperidine;

1-{[5-(2,4-dichlorophenyl)-1-(4-methoxyphenyl)-2-methyl-1*H*-pyrrol-3-yl]carbonyl}piperidine;

1-{[1-(4-chlorophenyl)-5-(2,4-dimethoxyphenyl)-2-methyl-1*H*-pyrrol-3-yl]carbonyl}piperidine;

1-{[5-(2,4-dimethoxyphenyl)-1-(4-methoxyphenyl)-2-methyl-1*H*-pyrrol-3-yl]carbonyl}piperidine;

and where applicable, optical isomers, tautomers, stereoisomers and racemates thereof as well as pharmaceutically acceptable salts and solvates thereof.

13. A compound of formula I as claimed in any previous claim for use as a medicament.

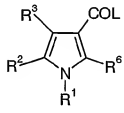
14. A pharmaceutical formulation comprising a compound of formula I, as defined in any one of claims 1 to 12 and a pharmaceutically acceptable adjuvant, diluent or carrier.

15. Use of a compound of formula I, as defined in any one of claims 1 to 12 including the compounds of the proviso in claim 1 in the preparation of a medicament for the treatment or prophylaxis of obesity, psychiatric disorders such as psychotic disorders, schizophrenia and bipolar disorders, anxiety, anxio-depressive disorders, depression, cognitive disorders, memory disorders, obsessive-compulsive disorders, anorexia, bulimia, attention disorders, epilepsy, and related conditions, and neurological disorders such as dementia, neurological disorders, Parkinson's Disease, Huntington's Chorea and Alzheimer's Disease, immune, cardiovascular, reproductive and endocrine disorders, septic shock, diseases related to the respiratory and gastrointestinal systems, and extended abuse, addiction and/or relapse indications.

16. A method of treating obesity, psychiatric disorders such as psychotic disorders, schizophrenia and bipolar disorders, anxiety, anxio-depressive disorders, depression, cognitive disorders, memory disorders, obsessive-compulsive disorders, anorexia, bulimia, attention disorders, epilepsy, and related conditions, and neurological disorders such as dementia, neurological disorders, Parkinson's Disease, Huntington's Chorea and Alzheimer's Disease, immune, cardiovascular, reproductive and endocrine disorders, septic shock, diseases related to the respiratory and gastrointestinal systems, and extended abuse, addiction and/or relapse indications, comprising administering a pharmacologically effective amount of a compound as claimed in any one of claims 1 to 12 including the compounds of the proviso in claim 1 to a patient in need thereof.

17. A compound as defined in any one of claims 1 to 12 including the compounds of the proviso in claim 1 for use in the treatment of obesity.

18. A process for the preparation of compounds of formula I in which X is CO comprising reacting a compound of formula III



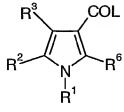
III

in which R^1, R^2, R^3, and R^6 are as previously defined and L represents hydroxy or halo with an amine of formula IV

$$R^4R^5YNH_2 \qquad IV$$

in which R^4 and R^5 are as previously defined in an inert solvent and optionally in the presence of a catalyst or optionally in the presence of a base at a temperature in the range of -25°C to 150°C, and when L is hydroxy optionally in the presence of a coupling agent.

19. A compound of formula III



III

in which R^1, R^2, R^3, and R^6 are as previously defined and L represents hydroxy or halo.

20. A compound selected from one or more of the following:

Ethyl 2-methyl-1,5-diphenyl-1*H*-pyrrole-3-carboxylate

Ethyl 1-(4-chlorophenyl)-2-methyl-5-phenyl-1*H*-pyrrole-3-carboxylate

Ethyl 1-(4-methoxyphenyl)-2-methyl-5-phenyl-1*H*-pyrrole-3-carboxylate

Ethyl 5-(2,4-dichlorophenyl)-2-methyl-1-phenyl-1*H*-pyrrole-3-carboxylate

Ethyl 1-(4-chlorophenyl)-5-(2,4-dichlorophenyl)-2-methyl-1*H*-pyrrole-3-carboxylate

Ethyl 5-(2,4-dichlorophenyl)- 1-(4-methoxyphenyl)-2-methyl-1*H*-pyrrole-3-carboxylate

Ethyl 5-(2,4-dimethoxyphenyl)-2-methyl-1-phenyl-1*H*-pyrrole-3-carboxylate

Ethyl 1-(4-chlorophenyl)-5-(2,4-dimethoxyphenyl)-2-methyl-1*H*-pyrrole-3-carboxylate

Ethyl 5-(2,4-dimethoxyphenyl)-1-(4-methoxyphenyl)-2-methyl-1*H*-pyrrole-3-carboxylate

2-Methyl-1,5-diphenyl-1*H*-pyrrole-3-carboxylic acid

1-(4-Chlorophenyl)-2-methyl-5-phenyl-1*H*-pyrrole-3-carboxylic acid

5-(2,4-Dichlorophenyl)-2-methyl-1-phenyl-1*H*-pyrrole-3-carboxylic acid

1-(4-Chlorophenyl)-5-(2,4-dichlorophenyl)-2-methyl-1*H*-pyrrole-3-carboxylic acid

5-(2,4-Dichlorophenyl)-1-(4-methoxyphenyl)-2-methyl-1*H*-pyrrole-3-carboxylic acid

5-(2,4-Dimethoxyphenyl)-2-methyl-1-phenyl-1*H*-pyrrole-3-carboxylic acid

1-(4-Chlorophenyl)-5-(2,4-dimethoxyphenyl)-2-methyl-1*H*-pyrrole-3-carboxylic acid and

5-(2,4-Dimethoxyphenyl)-1-(4-methoxyphenyl)-2-methyl-1*H*-pyrrole-3-carboxylic acid.

21. A compound as defined in any one of claims 1 to 12 combined with another therapeutic agent that is useful in the treatment of disorders associated with the development and progress of obesity such as hypertension, hyperlipidaemias, dyslipidaemias, diabetes and atherosclerosis.

INTERNATIONAL SEARCH REPORT

Internatic pplication No
PCT/GB 03/05569

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/402 A61K31/4025 A61K31/454 C07D207/34

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, BEILSTEIN Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 98 32441 A (SANOFI SA ;MARUANI JEANNE (FR); SOUBRIE PHILIPPE (FR)) 30 July 1998 (1998-07-30) the whole document ---	1-21
Y	WO 01 58869 A (PANDIT CHENNAGIRI R ;SQUIBB BRISTOL MYERS CO (US); WROBLESKI STEPH) 16 August 2001 (2001-08-16) cited in the application page 9, line 8 -page 11, line 19 ---	1-21
P,X	WO 03 027069 A (KLUENDER HAROLD C E ;FAN JIANMEI (US); LAVOIE RICO C (US); SMITH R) 3 April 2003 (2003-04-03) the whole document --- -/--	1-21

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
12 March 2004	23/03/2004

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Fink, D

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	WO 01 47880 A (ICOS CORP) 5 July 2001 (2001-07-05) page 112 -page 113; claim 1 page 71; example 44 ---	19,20
X	SCALZO M ET AL: "RICERCHE SU SOSTANZE AD ATTIVITA ANTIBATTERICA ED ANTIFUNGINA NOTA IV - SINTESI ED ATTIVITA MICROBIOLOGICA DI NUOVI DERIVATI 1,5-DIARILPIRROLICI" FARMACO, SOCIETA CHIMICA ITALIANA, PAVIA, IT, vol. 43, no. 9, September 1988 (1988-09), pages 665-676, XP000945201 ISSN: 0014-827X cited in the application page 668, the compounds (V) and (VI) page 669; table II, the compound (IVb) page 670; table III, the compounds (Vb) and (Vc) page 670; the penultimate paragraph, the method for preparing the 1,5-diaryl-2-methyl-pyrrole-3-carboxylic acid chlorides of general formula (VI) ---	19,20
X	PETRUSO S ET AL: "OXIDATIVE HALOGENATION OF SUBSTITUTED PYRROLES WITH CU(II). PART II. BROMINATION OF SOME ETHYL 3-PYRROLECARBOXYLATES AND CORRESPONDING ACIDS" JOURNAL OF HETEROCYCLIC CHEMISTRY, HETEROCORPORATION. PROVO, US, vol. 27, no. 5, July 1990 (1990-07), pages 1277-1280, XP000945179 ISSN: 0022-152X page 1277; table 1, the compounds VIII and XI ---	19,20
X	PORRETTA G C ET AL: "RICERCHE SU SOSTANZE AD ATTIVITA ANTIBATTERICA ED ANTIFUNGINA NOTA VII - SINTESI ED ATTIVITA MICROBIOLOGICA DE NUOVI DERIVATI DELL'1,5-DIARILPIRROLO" FARMACO, SOCIETA CHIMICA ITALIANA, PAVIA, IT, vol. 44, no. 1, January 1989 (1989-01), pages 65-76, XP000945349 ISSN: 0014-827X cited in the application page 69, the compounds of table II page 69; the last paragraph, the method for preparing the 1,5-diaryl-2-methyl-pyrrole-3-carboxylic acid chlorides starting from the acids of general formula (IV) --- -/--	19

INTERNATIONAL SEARCH REPORT

Internatic pplication No
PCT/GB 03/05569

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	SCALZO M ET AL: "RICERCHE SU SOSTANZE AD ATTIVITA ANTIBATTERICA ED ANTIFUNGINA" FARMACO, SOCIETA CHIMICA ITALIANA, PAVIA, IT, vol. 43, no. 9, September 1988 (1988-09), pages 677-691, XP000945203 ISSN: 0014-827X cited in the application page 680, the compounds (V) and (VI) page 682; table II, the compounds (V2), (V3), (V5), (V6), (V8), (V9), (V11), (V12), (V14), (V15) page 681; the last paragraph, the method for preparing the 1,5-diaryl-2-methyl-pyrrole-3-carboxylic acid chlorides of general formula (VI) -----	19

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/GB 03/05569

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claim 16 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [X] Claims Nos.: 1-11 (all partly), 13-19 (all partly), and 21 (partly)
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

see FURTHER INFORMATION sheet PCT/ISA/210

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 1-11 (all partly), 13-19 (all partly), and 21 (partly)

The initial phase of the search revealed a very large number of documents relevant to the issue of novelty. So many documents were retrieved that it is impossible to determine which parts of the claims may be said to define subject-matter for which protection might legitimately be sought (Article 6 PCT). For these reasons, a meaningful search over the whole breadth of the claims is impossible. Consequently, the search has been restricted to the compounds of the general formula II (cf., the present claim 6) and those compounds of the general formula III (cf., the present claim 19) wherein R1, R2, R3, and R6 are defined as in claim 6.

It is further noted that the expression "prodrugs" as used in the present claims 1-11 is considered to be unclear in the sense of Article 6 PCT. This expression does not comprise any information as regards the structure of the compounds concerned. It is therefore impossible to compare the said prodrug compounds with what is set out in the prior art. The lack of clarity is such as to render a meaningful complete search impossible. Consequently, the said "prodrugs" have not been searched.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Application No
PCT/GB 03/05569

Patent document cited in search report		Publication date	Patent family member(s)		Publication date
WO 9832441	A	30-07-1998	FR	2758723 A1	31-07-1998
			AU	6219398 A	18-08-1998
			BR	9806801 A	16-05-2000
			CA	2278661 A1	30-07-1998
			EE	9900304 A	15-02-2000
			EP	0969835 A1	12-01-2000
			WO	9832441 A1	30-07-1998
			HR	980042 A1	31-10-1998
			ID	22216 A	16-09-1999
			JP	2001501971 T	13-02-2001
			LV	12354 A	20-10-1999
			LV	12354 B	20-02-2000
			NO	993634 A	27-09-1999
			SK	99799 A3	12-06-2000
			TR	9901721 T2	21-10-1999
			TW	450808 B	21-08-2001
			US	2002128302 A1	12-09-2002
			US	6344474 B1	05-02-2002
			ZA	9800691 A	05-08-1998
WO 0158869	A	16-08-2001	AU	3495801 A	20-08-2001
			CA	2399791 A1	16-08-2001
			EP	1254115 A2	06-11-2002
			JP	2004502642 T	29-01-2004
			WO	0158869 A2	16-08-2001
			US	2002119972 A1	29-08-2002
WO 03027069	A	03-04-2003	WO	03027069 A1	03-04-2003
WO 0147880	A	05-07-2001	AU	1087101 A	09-07-2001
			CA	2395543 A1	05-07-2001
			CN	1434799 T	06-08-2003
			EP	1244620 A1	02-10-2002
			JP	2003519123 T	17-06-2003
			WO	0147880 A1	05-07-2001
			US	2003013754 A1	16-01-2003
			US	6372777 B1	16-04-2002